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Application No.: 10/649,944  
Office Action Dated: December 15, 2005

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### REMARKS

Following entry of the foregoing amendments, claims 1, 3 to 11, 13 to 17, 19, and 20 will be pending in the application. Claims 1, 3, and 7 to 9 have been amended, and claims 2, 12, and 18 have been canceled, herein, without prejudice. No new claims have been added. Support for the amendments is found throughout the specification as originally filed. No new matter has been added.

Applicants respectfully request reconsideration of the rejections of record in view of the foregoing amendments and the following remarks.

#### Alleged Lack of Written Description

Claim 18 has been rejected under 35 U.S.C. § 112, first paragraph for lack of written description because the subject matter recited in the claim, treatment of large cell lymphoma, is allegedly not described in the specification as originally filed. Without conceding the correctness of the rejection, and to advance prosecution, claim 18 has been canceled, obviating the rejection.

#### Alleged Anticipation

Claims 1 to 8 and 12 have been rejected under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent No. 6,720,011 ("the Zhang patent"). The Office action asserts that the Zhang patent describes treatment of lymphoma with arsenic trioxide. Applicants respectfully request reconsideration and withdrawal of the rejection because the Zhang patent fails to demonstrate that arsenic trioxide is efficacious for the treatment of lymphoma.

The Zhang patent describes arsenic trioxide compositions and states that they can be used to treat cancers that include lymphoma<sup>1</sup>, but fails to provide any guidance whatsoever as to the efficacy of the compositions for lymphoma treatment. The patent's single working example describes the use of arsenic trioxide compositions for the treatment of a particular type of leukemia (acute promyelocytic leukemia)(col. 2, ln. 59 to col. 3, ln. 27). In addition, the patent's

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<sup>1</sup> "The present invention is directed to an intravenous drip composition for the treatment of cancers. The cancers treatable include leukemia, hepatoma and lymphoma." (col. 1, lns. 33 to 35).

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description of the effect of the described arsenic trioxide compositions on cancer cells is limited to a description of its effect on leukemia cells:

Laboratory experiments indicate that the composition shows a strong abruptive effect on the membranes of leukemic cells. It also inhibits DNA/RNA synthesis in such cells, reduces the rate of proliferation of leukemic cells and destroys the leukemic cells.

(col. 2, lns. 23 to 27). Accordingly, as understood by those skilled in the art, the Zhang patent fails to actually teach that arsenic trioxide is efficacious for the treatment of lymphoma.

Although the Office action asserts that the Zhang patent teaches that arsenic trioxide has a "strong abruptive effect on the membranes of cancer cells" and inhibits DNA and RNA synthesis,<sup>2</sup> the patent is referring to arsenic trioxide's effects on leukemia cells, rather than cancer cells generally:

Experimental results demonstrate that the intravenous composition of the present invention exert [*sic*] a strong abruptive effect on the membranes of cancer cells, such as leukemic cells. It inhibits DNA/RNA synthesis and reduces the proliferation of the leukemic cells.<sup>3</sup>

Because those skilled in the art would not understand arsenic trioxide to be effective for the treatment of lymphoma based upon the description provided in the Zhang patent, Applicants respectfully request withdrawal of the rejection.

#### Alleged Obviousness

A. Claims 9 to 11 and 13 to 20 have been rejected under 35 U.S.C. § 103(a) as allegedly obvious over the Zhang patent in view of Chinese Patent Number CN 1121807 ("the 807 patent") and Shimotsuura, S., *Journal of Tokyo Dental College Society*, 1986, 86(8) 1237-1253 ("the Shimotsuura article"). Applicants respectfully request reconsideration and withdrawal of the rejection because the office action has failed to establish *prima facie* obviousness.

To establish *prima facie* obviousness, the Patent Office must provide objective evidence that the prior art relied upon, coupled with the knowledge generally available in the art at the

<sup>2</sup> Office action dated December 15, 2005, page 3.

<sup>3</sup> Col. 1, lns. 58 to 62.

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time of the invention, contains some suggestion or incentive that would have motivated those of ordinary skill in the art to modify a reference or to combine references. *In re Lee*, 61 U.S.P.Q.2d 1430, 1433 (Fed. Cir. 2002); *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1998). And the proposed modification or combination of the prior art ***must have had a reasonable expectation of success***, determined from the vantage point of those of ordinary skill in the art, at the time the invention was made. *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991).

“[W]hether a particular combination might be ‘obvious to try’ is not a legitimate test of patentability.” *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988). “Obvious to try” situations arise where it might have been obvious to “explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.” *In re O’Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). *See also Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1380 (Fed. Cir. 1986)(stating that “At most, these articles are invitations to try monoclonal antibodies in immunoassays but do not suggest how that end might be accomplished.”)(emphasis in original).

Upon review of the references cited in the Office action, those skilled in the art would not have reasonably expected at the time of the invention that arsenic trioxide could have been successfully used to treat lymphoma in humans. At most, it might have been obvious to persons skilled in the art *to try* to use arsenic trioxide to treat lymphoma, but much more is required for *prima facie* obviousness.

As discussed above, the Zhang patent describes treatment of leukemia with arsenic trioxide and provides results demonstrating its efficacy for the treatment of acute promyelocytic leukemia. The patent fails to provide any guidance as to the efficacy of arsenic trioxide for the treatment of lymphoma, however. Similarly, the 807 patent describes the efficacy of Ai Ling, which contains arsenic trioxide, sodium chloride, and water, for the treatment of leukemia. Although the patent states that Ai Ling can be used to treat lymphatic cancer, it provides no indication as to its efficacy for doing so. Notably, the patent describes the effects that Ai Ling has against leukemia cells, but makes no mention of its effect against lymphatic cancer cells:

Tests have proven that this drug has strong effects on the destruction of leukemia cell membranes, inhibiting DNA and RNA synthesis and loss of ability of clone

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proliferation; in vivo and in vitro tests have verified that it possessed marked killing effects against leukemia cells; it also has effects which induce the leukemia cells to differentiate to normal cells; it is able to promote the restoration of bone marrow hemopoietic functions...<sup>4</sup>

In addition, the experimental examples provided in the patent describe the effects of administering Ai Ling to patients suffering from acute promyelocytic leukemia, not to patients suffering from lymphatic cancers.

Moreover, the Shimotsuura article describes the efficacy of arsenic trioxide in a mouse sarcoma model and indicates that arsenic trioxide was only efficacious when it was coadministered with an antidote. The article fails to describe or suggest the treatment of lymphomas with arsenic trioxide. Although the Office action asserts that the article teaches that "antineoplastic [sic] actions of arsenic trioxide are primarily achieved by DNA composition blockage,"<sup>5</sup> the article states that the DNA composition blockage occurred in S-180 (sarcoma) cells transplanted into mice, and does not teach that DNA composition blockage occurs in cancerous cells other than sarcoma cells:

From above results,  $As_2O_3$  is considered that can increase life span of the mouse by blocking DNA composition of S-180 cells and protein composition.<sup>6</sup>

The references cited in the Office action thus fail to teach or suggest that arsenic trioxide can be successfully used in humans to treat lymphoma. Rather, the references teach that arsenic trioxide is effective in humans against acute promyelocytic leukemia and suggest that it may be effective against sarcomas when administered in conjunction with an antidote. Those skilled in the art would have appreciated at the time of the invention that the efficacy of a particular anti-cancer agent against a specific type of cancer was not predictive of its efficacy against other types of cancers. It was understood that "[i]ncreasingly disease-specific therapies are being developed that will have optimum application for only one tumor type, although representing ineffective and toxic treatment for others."<sup>7</sup> Indeed, the therapeutic agents most commonly used to treat cancers at the time of the invention (and at present, as well) were effective only against

<sup>4</sup> Page 5 of the English translation.

<sup>5</sup> Office action dated December 15, 2005, page 5.

<sup>6</sup> Page 20 of the English translation.

<sup>7</sup> *Medical Oncology*, Calabresi, P., et al., eds., 1985, Macmillan Publishing Company, page 257 (copy enclosed as Exhibit A).

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specific types of cancers, and generally did not exhibit broad efficacy against numerous cancer types.<sup>8</sup> Accordingly, those skilled in the art would not have reasonably expected that arsenic trioxide could have been successfully used to treat lymphoma in humans just because it had been reported to have efficacy in humans against acute promyelocytic leukemia. At most, those skilled in the art might have considered trying to use arsenic trioxide to treat cancers in humans other than acute promyelocytic leukemia, but the results of doing so could not have been predicted with a reasonable degree of certainty. Accordingly, those skilled in the art at the time of the invention would not have reasonably expected that arsenic trioxide could have been successfully used to treat lymphoma in humans.

Although the Office action asserts that "since all of the lymphomas recited in applicant's claims are cancers of the lymphatic system with uncontrolled growth of cells of similar functions and origin, one having ordinary skill in the art would have been motivated to administer arsenic trioxide to treat such lymphomas, particularly in view of its adverse effect on rapid DNA replication,"<sup>9</sup> as discussed above, however, even if those skilled in the art would have been so motivated, they would not have had a reasonable expectation of success for such an endeavor. Due to the nature of cancer, and methods for its treatment and management at the time of the invention, those skilled in the art would not have reasonably expected that an agent shown to be effective against acute promyelocytic leukemia could have been successfully used to treat lymphoma in humans. Notably, the chemotherapeutic agent busulfan was known at the time of the invention to be effective against chronic granulocytic leukemia and methotrexate was known to be effective against acute lymphocytic leukemia, but neither agent was known to be effective against lymphoma, while carmustine and lomustine were each known at the time of the invention to be efficacious against lymphoma, but were not known to be effective against any type of leukemia,<sup>10</sup> illustrating the uncertainty in the art as to the efficacy of particular anti-cancer agents against different types of cancers.

The Office action has, therefore, failed to establish *prima facie* obviousness, and Applicants, accordingly, respectfully request withdrawal of the rejection.

<sup>8</sup> *Id.* at 295-297 (copy enclosed as Exhibit A).

<sup>9</sup> Office action dated December 15, 2005, page 6.

<sup>10</sup> *Medical Oncology*, Calabresi, P., *et al.*, eds., 1985, Macmillan Publishing Company, page 295 (copy enclosed as Exhibit A).

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B. Claims 9 to 11 and 13 to 20 have been rejected under 35 U.S.C. § 103(a) as allegedly obvious over the Zhang patent in view of the 807 patent, Li, Y., *et al.*, *Chinese J. Oncology*, 1988, 10, 61-62 ("the Li article") and the Shimotsuura article. Applicants respectfully request reconsideration and withdrawal of the rejection because the office action has failed to establish *prima facie* obviousness.

As discussed above, based upon the teachings of the Zhang and 807 patents and the Shimotsuura article, those skilled in the art at the time of the invention would not have reasonably expected that arsenic trioxide could have been successfully used to treat lymphoma in humans. The Li article would not have changed the thinking of those skilled in the art in this regard. The article describes the treatment of patients suffering from various lymphomas with "Ailin-1" in combination with Chinese herbal medicines. The English translation of the article does not indicate what "Ailin-1" is, nor does it identify the Chinese herbal medicines that were administered to the patients. The composition of the "Ailin-1" used in the reported studies could thus not have been known with certainty at the time of the invention due to the fact that its ingredients are not specified in the article<sup>11</sup>. In addition, those skilled in the art would have appreciated that the unspecified Chinese herbal medicines administered to the patients, rather than the Ailin-1, could actually have been responsible for the reported remission in the patients' malignant lymphoma. Accordingly, based upon the teachings of the Li reference, those skilled in the art at the time of the invention would likely have doubted whether arsenic trioxide could have been successfully used to treat lymphoma in humans.

Because those skilled in the art would not have reasonably expected that arsenic trioxide could have been successfully used to treat lymphoma in humans upon review of the Zhang and 807 patents and the Shimotsuura and Li articles, the Office action has failed to establish *prima facie* obviousness, and Applicants accordingly, respectfully request withdrawal of the rejection.

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<sup>11</sup> The English translation provided with the article does not specify the composition of Ailin-1.  
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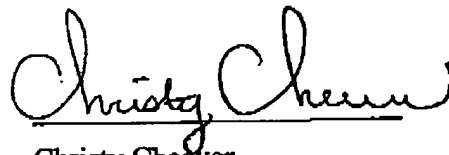
**Information Disclosure Statement**

In response to the Examiner's request for clarification as to which of the search reports cited in the Form PTO 1449 filed with this application was issued in connection with the corresponding European application, the "International Search Report of EP 03019628" was issued in connection with the counterpart European application.

**Conclusion**

Applicants believe that the foregoing constitutes a complete and full response to the Office action of record. An early and favorable action is accordingly, respectfully requested.

Respectfully submitted,



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Date: April 12, 2006

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